

Alkaline phosphatase in metastatic castration-resistant prostate cancer: reassessment of an older biomarker

Daniel Heinrich^{*1}, Øyvind Bruland², Theresa A Guise³, Hiroyoshi Suzuki⁴ & Oliver Sartor⁵

¹Department of Oncology, Akershus University Hospital, Sykehusveien 25, 1478 Lørenskog, Norway

²Department of Oncology, Oslo University Hospital–Norwegian Radium Hospital, Ullernchaussen 70, 0379 Oslo, Norway

³Department of Medicine, Indiana University School of Medicine, 980 W. Walnut St, Walther Hall, R3, Room C130 Indianapolis, IN 46202, USA

⁴Department of Urology, Toho University Sakura Medical Center, 564-1 Shimazu, Sakura-shi, Chiba 285-8741, Japan

⁵Departments of Medicine & Urology, Tulane Cancer Center, 1430 Tulane Ave., SL-42, New Orleans, LA 70112, USA

*Author for correspondence: Tel.: +47 913 95554; daniel.heinrich@ahus.no

Since most patients with metastatic castration-resistant prostate cancer (mCRPC) have bone metastases, it is important to understand the potential impact of therapies on prognostic biomarkers, such as ALP. Clinical studies involving mCRPC life-prolonging agents (i.e., sipuleucel-T, abiraterone, enzalutamide, docetaxel, cabazitaxel, and radium-223) have shown that baseline ALP level is prognostic for overall survival, and may be a better prognostic marker for overall survival than prostate-specific antigen in patients with bone-dominant mCRPC. Mechanism of action differences between therapies may partly explain ALP dynamics during treatment. ALP changes can be interpreted within the context of other parameters while monitoring disease activity to better understand the underlying pathology. This review evaluates the current role of ALP in mCRPC.

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Prostate cancer has a propensity to metastasize to the bone and locally disrupt normal bone remodeling [1,2]. Bone metastases develop through hematogenous dissemination, predominantly to the red marrow elements of the axial skeleton, where they cause an imbalance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation [3]. In prostate cancer, bone metastases are predominantly characterized by an osteoblastic phenotype, with evidence of increased bone formation and sclerosis on radiography [4–6]. Enhanced osteoclastic bone resorption is also common. Since approximately 90% of patients with metastatic castration-resistant prostate cancer (mCRPC) have radiologic evidence of bone metastases [7,8], it is important to understand the mechanisms of bone disease and the potential impact of therapies on prognostic biomarkers, such as ALP.

This review examines the sources and prognostic value of ALP in bone-dominant mCRPC, and presents guidance on the value of ALP as a biomarker in mCRPC. Furthermore, it describes the mechanisms of action of survival-prolonging drugs in mCRPC, specifically regarding the potential impact on ALP dynamics; evaluates ALP data from clinical trials of agents that confer a survival advantage in mCRPC; and considers whether different therapy mechanisms of action can explain ALP clinical data.

ALP in bone-metastatic CRPC

ALP originates primarily from the liver and bone [3], with bone-specific ALP (bALP) accounting for 40–50% of ALP levels in healthy adults. bALP is an enzyme that is expressed on the surface of osteoblasts [1]. It contributes to the mineralization of newly laid type 1 collagen-rich bone matrix, and its expression mirrors an osteoblastic stroma undergoing microcalcification [9]. Increased bALP levels can indicate either a disease state or healing that is occurring within the bone [9].

bALP level is used as a bone turnover marker reflective of a combination of osteoblastic activity and extent of disease (i.e., volume of metastases) in patients with bone-dominant mCRPC [1,4]. As bone metastases develop, bALP is released into the blood and urine [3]. In the absence of extensive liver disease, bALP is the primary component of serum total ALP (tALP) levels measured in patients with mCRPC [10]. bALP can be used as a serum marker of increased osteoblast activity, with its secretion indicating the presence of proliferating osteoblasts.

Cross-talk between tumor cells and the bone microenvironment disrupts normal bone remodeling, leading to a 'vicious cycle', as explained below, which further fuels tumor growth in bone [1,2,11,12]. Sources of ALP in the pathologic state are not fully known, but it is thought to originate primarily from increased activation of osteoblasts, with potentially direct expression also in prostate cancer cells [13,14]. Prostate cancer bone metastases activate osteoblasts, leading to the release of ALP during new bone formation. Prostate cancer cells also secrete factors that activate stromal cells in the bone microenvironment and stimulate osteoblast activity [4]. For example, bone morphogenetic proteins and sonic hedgehog provide a favorable environment for the growth and survival of prostate cancer cells, promoting osteoblast differentiation and expression of osteoblastic markers, including ALP [4].

Prostate cancer cells can develop an osteoblast-like cell phenotype within the bone microenvironment, potentially contributing directly to increased ALP levels [13,14]. Bone-metastatic prostate cancer cells are osteomimetic, may develop osteoblastic properties through independent activation of ERK and Notch signaling, and are capable of expressing genes and proteins typically expressed by osteoblasts [5]. Cross-talk between prostate tumor cells and osteoblasts promotes osteomimicry [15], a condition in which prostate cancer cells achieve stem cell properties of bone marrow mesenchymal stem cells and often express osteoblastic markers [16]. For example, the C4-2B human prostate cancer cell line that metastasizes to bone has attributes of an osteoblast phenotype not present in the parental LNCaP cell line, which does not metastasize to the bone [14]. C4-2B cells are able to induce mineralization and gain an osteoblast phenotype that produces ALP *in vitro*, suggesting (but not proving) that prostate cancer cells in bone metastases contribute directly to the mineral formation found in osteoblastic lesions and the bALP levels in serum.

Clinical importance of ALP

ALP is a prognostic biomarker in mCRPC, reflecting disease outcome independent of therapy [17]. Measuring tALP levels is inexpensive and readily available. In patients with mCRPC, high baseline ALP levels are associated with negative outcomes, including skeletal complications and decreased survival [18–20]. Moreover, elevated ALP levels have also been correlated with the extent of metastatic bone disease [12,20]. Changes in ALP levels may reflect changes in bone turnover and osteoblastic activity.

The use of baseline ALP level as a prognostic marker for overall survival (OS) in patients with mCRPC has been confirmed in multivariate analyses and multiple prognostic models independent of therapy selection [21–24]. Importantly, baseline ALP is a relevant prognostic marker for OS in bone-dominant mCRPC, along with others (e.g., prostate-specific antigen [PSA]) [7,25]. Studies of ALP after treatment are more limited, and the utility of changes in ALP as a marker post-therapy has yet to be completely explored.

A retrospective study that evaluated whether ALP kinetics were prognostic for bone metastasis and death in patients with CRPC indicated that ALP velocity (the slope of the linear regression line of all ALP values overtime) was an independent prognostic factor for OS and bone metastases-free survival in mCRPC patients [26]. Similar findings were observed in an independent dataset [27]. Monitoring ALP levels in mCRPC can provide prognostic information about the likely outcome of the disease [28], but changes in ALP have not been validated as a surrogate for effectiveness of mCRPC therapy [29].

Mechanism of action impact on ALP levels

Six drugs are currently approved for the treatment of mCRPC, based on their ability to prolong survival versus placebo or active comparator in Phase III clinical trials: sipuleucel-T, abiraterone acetate, enzalutamide, docetaxel, cabazitaxel, and radium-223 dichloride. These survival-prolonging drugs have their unique mechanisms of action that correspond to different effects on ALP levels during treatment, and they represent opportunities for sequencing and combination strategies in mCRPC treatment, although combinations have yet to be proven effective. The mechanism of action for each drug and potential impact on ALP levels are summarized in Table 1 [30–62].

Table 1. Mechanism of action and impact on alkaline phosphatase levels for survival-prolonging metastatic castration-resistant prostate cancer drugs.

Survival-prolonging mCRPC drugs	Drug class	US FDA-approved indication	Mechanism of action	Impact on ALP levels in patients with mCRPC	Ref.
Sipuleucel-T	Immunotherapy	For the treatment of asymptomatic or minimally symptomatic mCRPC	Autologous cellular immunotherapy	Clinical impact on ALP levels not likely	[30–34]
Abiraterone acetate (abiraterone)	Hormonal therapy	In combination with prednisone for treatment of patients with mCRPC	CYP17 inhibitor	Indirect effect: ALP levels decrease as tumor burden decreases	[35–40]
Enzalutamide	Hormonal therapy	For treatment of patients with mCRPC	Androgen receptor inhibitor	Indirect effect: ALP levels decrease as tumor burden decreases	[41–44]
Docetaxel	Taxane chemotherapy	In combination with prednisone for treatment of patients with mCRPC	Microtubule inhibitor	Indirect effect: ALP levels decrease as tumor burden decreases	[45–50]
Cabazitaxel	Taxane chemotherapy	In combination with prednisone for treatment of patients with mCRPC previously treated with a docetaxel-containing treatment regimen	Microtubule inhibitor	Indirect effect: ALP levels decrease as tumor burden decreases	[51–54]
Radium-223 dichloride (radium-223)	Targeted alpha therapy	For treatment of patients with CRPC, symptomatic bone metastases, and no known visceral metastatic disease	α -particle emission	Direct effect: ALP levels decrease as bone formation is reduced via microenvironmental effect	[55–62]

CRPC: Castration-resistant prostate cancer; mCRPC: Metastatic castration-resistant prostate cancer.

Immunotherapy

Sipuleucel-T

Sipuleucel-T is an autologous cellular immunotherapy that uses a patient's own cells to stimulate an immune response against prostatic acid phosphatase to target and remove prostate cancer cells, thereby inducing a systemic immune response against the patient's prostate cancer cells that express prostatic acid phosphatase (Table 1) [30–33]. The effect of sipuleucel-T may lead to antigen shedding, causing an even broader antitumor immune response [32]. The mechanism of action of sipuleucel-T does not suggest a direct impact on ALP levels when the agent is used to treat the patients with mCRPC [63].

Hormonal therapy

Abiraterone acetate

Abiraterone acetate (abiraterone) is a selective, irreversible inhibitor of CYP17 [35–39]. When hydrolyzed, this oral prodrug converts to its active metabolite abiraterone and inhibits androgen biosynthesis (Table 1). Abiraterone is taken with prednisone or prednisolone to address the imbalance of mineralocorticoid activity that occurs with CYP17 targeting. CYP17 is expressed during osteoclast and osteoblast maturation, and abiraterone has been shown to inhibit osteoclast maturation and also promote osteoblast differentiation and ALP upregulation in an *in vitro* study of human primary osteoclasts and osteoblasts [38]. Given its mechanism of action, abiraterone is not expected to directly decrease ALP levels when used to treat mCRPC patients; however, an indirect effect will likely occur as the tumor burden decreases and bone healing occurs. Clinical experience has shown that ALP levels may increase initially after starting abiraterone (e.g., first 2–6 weeks) and later decrease in mCRPC patients who respond to therapy. The initial increase is likely attributable to healing bone and is often noted in patients with a sharp decline in PSA levels.

Enzalutamide

Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway (Table 1) [41–43]. Enzalutamide competitively inhibits androgen binding to androgen receptors and inhibits androgen receptor nuclear translocation and interaction with DNA. It ultimately results in decreased cell growth and apoptosis of prostate cancer cells, leading to decreased mCRPC tumor volume [41–43]. The mechanism of action of enzalutamide is not expected to directly decrease ALP levels when the agent is used to treat mCRPC patients; however, an indirect effect will likely occur as the tumor burden decreases. As with abiraterone, clinical experience

has shown that ALP levels may increase initially after starting enzalutamide (e.g., first 2–6 weeks) and later decrease in mCRPC patients who respond to therapy. The mechanism underlying ALP change in enzalutamide-treated patients is likely similar to that of abiraterone. Initial increases in ALP are likely due to healing bone; subsequent decreases occur over time as bone remodeling diminishes as a consequence of antitumor activity.

Taxane chemotherapies

Docetaxel

Docetaxel is a semisynthetic taxane, with several mechanisms of action being proposed to account for its antineoplastic activity in prostate cancer (Table 1) [45–49]. Most notably, docetaxel disrupts mitosis, promoting apoptotic cell death [45–47]. It is also thought to affect androgen signaling in prostate cancer cells, leading to downregulation of androgen receptors and decreased secretion of PSA [47–49]. Given its mechanism of action, the effects of docetaxel on ALP are indirect, with changes in the tumor causing alterations in ALP levels via the microenvironmental changes that occur as a function of antitumor effects. ALP ‘flares’, as seen with abiraterone and enzalutamide during the first weeks of treatment, are less common during treatment with docetaxel.

Cabazitaxel

Cabazitaxel is a semisynthetic taxane whose antitumor mechanism of action is similar to that of docetaxel (Table 1) [51–53]. It is structurally distinct from docetaxel, with a slightly larger biochemical structure. Unlike other taxanes, cabazitaxel has a low affinity for P-glycoprotein 1, a drug efflux pump thought to contribute to docetaxel resistance [51–53]. As with docetaxel, cabazitaxel’s mechanism of action suggests an indirect effect on ALP levels.

Targeted alpha therapy

Radium-223 dichloride

Radium-223 dichloride (radium-223) is a targeted alpha therapy that mimics calcium to accumulate in sites of active bone remodeling (Table 1) [55–60]. It emits high-energy, short-range (<100 µm) α particles to induce double-stranded DNA breaks in target cells. Prostate cancer models have shown that radium-223 induces such DNA damage in tumor cells, osteoblasts, and osteoclasts, suggesting direct radiation effects on both tumor and bone microenvironment during osseous tumor growth [59]. This dual-targeting mechanism of action inhibits disease progression through cytotoxic effects on tumor cells and stabilization of the bone microenvironment in bone metastases. Similar findings were observed in a mouse model of breast cancer bone metastases, suggesting efficacy regardless of primary tumor origin [60]. Radium-223 has also been shown to be associated with immunogenic cell death *in vitro* in human prostate cancer cell lines, but the contribution of this effect *in vivo* is unknown [61]. The radium-223 mechanism of action reduces bone formation, directly decreasing ALP levels during treatment in mCRPC patients. Clinical experience has shown that ALP levels decrease rapidly and usually without any ‘flare’ after initiation of radium-223 treatment, but increase again after completion of the therapeutic regimen [64–66].

Denosumab & zoledronic acid

The bone-targeting agents denosumab and zoledronic acid are distinct from the six survival-prolonging drugs mentioned above (Table 1), in that clinical studies have not demonstrated a survival benefit when these drugs are used to treat patients with mCRPC [6]. Their use as supportive agents in patients with mCRPC does impact ALP levels, and because most patients will receive denosumab or zoledronic acid in addition to survival-prolonging anticancer drugs, their mechanisms of action and potential impact on ALP levels are worth noting. During treatment, changes in ALP levels will likely be driven both by denosumab or zoledronic acid and by the survival-prolonging anticancer drugs, and probably to different extents.

Denosumab binds to RANKL, preventing the binding of RANKL to RANK, thus inhibiting the formation and activation of osteoclasts. Zoledronic acid binds to mineralized bone matrix and reduces osteoclast activity by inducing osteoclast apoptosis [6]. Since ALP levels increase when bone destruction is linked to bone formation (e.g., high-turnover osteoporosis), use of these bone resorption inhibitors in patients with mCRPC may contribute to decreased ALP levels.

ALP & life-prolonging mCRPC therapies

This section reviews results from trials involving drugs that have shown life-prolonging ability for patients with mCRPC, with a special emphasis on ALP data.

Table 2. Trials indicating a prognostic value for alkaline phosphatase level in overall survival of patients with metastatic castration-resistant prostate cancer treated with the survival-prolonging agents.

Trial [†]	Study design	n	Treatment	Prognostic factor	HR for OS (95% CI); p-value	Ref.
Sipuleucel-T						
George <i>et al.</i>	Pooled data from three Phase III trials	249	Crossover from control arm to sipuleucel-T	– Baseline ALP	– NA; independent predictor of postprogression survival (p < 0.1) [‡]	[67]
Bilen <i>et al.</i>	Retrospective analysis	56	Sipuleucel-T	– Baseline ALP (>90 vs ≤90 IU/l)	– 8.7 (1.7–46); p < 0.01 [‡]	[63]
Abiraterone acetate (abiraterone)						
Fizazi <i>et al.</i> (COU-AA-301 trial)	Phase III: patients previously treated with docetaxel (final analysis)	1195	Abiraterone + prednisone vs placebo + prednisone	– Baseline ALP >median – Baseline ALP <median	– 0.60 (0.50–0.74) – 0.88 (0.69–1.12)	[68]
Chi <i>et al.</i>	Prognostic model	762	Abiraterone + prednisone	– Baseline ALP (>ULN [160 IU/l] vs ≤ULN)	– 2.02 (1.69–2.41); p < 0.0001 [§] – 1.38; p = 0.0016 [‡]	[69]
Ryan <i>et al.</i> (COU-AA-302 trial)	Phase III: chemotherapy-naïve patients (final analysis)	1088	Abiraterone + prednisone vs placebo + prednisone	– Baseline ALP	– NA; significantly prognostic [‡]	[70]
Mikah <i>et al.</i>	Retrospective analysis	84	Abiraterone + prednisone	– Increase in baseline ALP after 12 wk (yes vs no) – No ALP flare vs ALP flare	– 4.9 (2.7–8.9); p < 0.001 [§] – 3.1 (1.7–5.7); p < 0.001 [§]	[71]
Docetaxel						
Armstrong <i>et al.</i> (TAX327 trial)	Multivariate model from Phase III trial	1006	Docetaxel + prednisone vs mitoxantrone + prednisone	– Baseline ALP	– 1.27 per log rise (1.15–1.39); p < 0.001 [‡]	[72]
Armstrong <i>et al.</i> (TAX327 trial)	Multivariate model from Phase III trial	604	Docetaxel + prednisone vs mitoxantrone + prednisone	– Baseline ALP (<200 vs 200–1000 IU/dl) – Baseline ALP (<200 vs >1000 IU/dl)	– 1.26 (1.02–1.55); p = 0.033 [‡] – 1.55 (1.11–2.21); p = 0.012 [‡]	[73]
Sonpavde <i>et al.</i> (TAX327 trial)	Retrospective analysis	601	Docetaxel + prednisone vs mitoxantrone + prednisone	– Normalization of ALP (<120 U/l) by day 90, adjusted for ≥30% PSA decrease – Any increase in ALP by day 90, adjusted for ≥50% PSA increase	– 0.79 (0.65–0.97); p = 0.022 [‡] – 1.64 (1.28–2.10); p < 0.001 [‡]	[74]
Cabazitaxel						
Bahl <i>et al.</i> (TROPIC trial)	2-year follow-up	755	Cabazitaxel + prednisone vs mitoxantrone + prednisone	– Baseline ALP	– [OR: 0.95 (0.92–0.98); p < 0.001] [‡]	[75]
van Soest (CABARESC trial)	Phase II (postdocetaxel)	114	Cabazitaxel + prednisone + budesonide vs cabazitaxel + prednisone	– Baseline ALP	– 1.84 (1.31–2.60); p < 0.001 [§] – 1.65 (1.06–2.57); p = 0.026 [‡]	[76]
Radium-223						
Sartor <i>et al.</i> (ALSYMPCA trial)	Phase III prognostic model	921	Radium-223 + BSoC vs placebo + BSoC [¶]	– Total ALP [#] – tALP decline	– 2.017; p < 0.0001 – 0.45 (0.34–0.61); p < 0.0001 [‡]	[65]

[†]Enzalutamide is not included because the literature search did not identify any trials or analyses that evaluated the prognostic value of ALP for overall survival.

[‡]Multivariate analysis.

[§]Univariate analysis.

[¶]Log transformation due to heavily skewed distribution (ten-fold increase).

[#]Overall intention to treat population.

BSoC: Best standard of care; HR: Hazard ratio; mCRPC: Metastatic castration-resistant prostate cancer; NA: Not available; OR: Odds ratio; OS: Overall survival; PSA: Prostate-specific antigen; ULN: Upper limit of normal.

Sipuleucel-T

Limited ALP data are available from trials with sipuleucel-T in mCRPC patients (Table 2 [63,65,67–76]) [63,67,77,78]. In the Phase III IMPACT trial [77], sipuleucel-T efficacy was observed in mCRPC patients regardless of baseline ALP level. In another Phase III trial (n = 127), although median baseline ALP values were reported, no additional ALP analyses or analysis of the prognostic value of this biomarker was reported [78]. However, two studies have demonstrated the prognostic value of ALP in sipuleucel-T-treated patients, including one study that investigated the impact of control-arm crossover to salvage immunotherapy in patients who progressed after completing one of three Phase III trials with sipuleucel-T [67]. In this study, multivariate analysis identified lower baseline ALP

values as a potential indicator of survival ($p < 0.1$). In another retrospective study of 56 CRPC patients treated with sipuleucel-T, multivariate analysis using a Cox proportional hazards regression model indicated that baseline ALP >90 U/l was significantly associated with worse OS ($p = 0.01$) [63]. There is a lack of data on ALP dynamics during sipuleucel-T treatment in the published literature.

Abiraterone acetate

Abiraterone clinical trials evaluated efficacy of the drug in mCRPC patients according to baseline ALP levels, and examined the potential of ALP as a prognostic biomarker [68–71,79–83]. The Phase III COU-AA-301 trial randomized patients with mCRPC previously treated with docetaxel to prednisone plus abiraterone or placebo [68,80]. Both interim (median: 12.8 months) [80] and final (median: 20.2 months) [68] analysis of data from this trial showed that abiraterone prolonged OS regardless of whether a patient had baseline ALP levels above or below the median: value (hazard ratio [HR] <1 for both ALP subgroups; Table 2). Using data from this trial, a univariate Cox model (HR: 2.02, 95% CI: 1.69–2.41; $p < 0.0001$) and multivariate Cox model with a stepwise procedure (HR: 1.38; $p = 0.0016$) indicated that baseline ALP ($>$ upper limit of normal [ULN; 160 IU/l] vs \leq ULN) was prognostic for OS [69]. Another exploratory analysis of the COU-AA-301 study that evaluated pain control found no difference in baseline ALP levels between treatment groups for patients with or without baseline pain [81]. However, the potential correlation between pain palliation and serum ALP was not analyzed.

The Phase III COU-AA-302 trial in chemotherapy-naïve patients with mCRPC patients indicated that the treatment effect of abiraterone on OS was favorable (both HRs <1.0), regardless of baseline ALP level, at both the interim [79,82] and final analyses [70]. Multivariate analysis also determined that baseline ALP was significantly prognostic for OS in these patients (Table 2) [70,79].

Another study retrospectively analyzed data from 84 patients with mCRPC treated for a median of 14 months with abiraterone plus prednisone [71]. According to univariate analysis, the absence of an increase in ALP levels during the first 2–4 weeks of abiraterone treatment (followed by a decline within 8 weeks) and rising ALP levels at 12 weeks, together with a lack of $\geq 50\%$ decrease in PSA, were prognostic indicators of a higher risk of progressive disease and poorer OS (Table 2). However, multivariate analysis only identified a lack of $\geq 50\%$ decrease in PSA as an independent predictor of OS [71]. In considering these results, it is important to note that prednisone can also reduce bone formation and ALP activity. The study did not recommend stopping abiraterone treatment if there was a lack of early PSA response, but did suggest following these patients closely.

A retrospective cohort study of mCRPC patients used a Cox proportional hazards model to analyze the association between clinical features and the duration of drug exposure [83]. According to univariate analysis, the association between low ALP levels and treatment duration failed to reach significance (HR: 1.07, 95% CI: 0.99–1.16; $p = 0.074$) [83]. In summary, these studies demonstrate that baseline ALP is a strong prognostic indicator of OS in mCRPC patients treated with abiraterone.

Enzalutamide

ALP data from trials with enzalutamide in mCRPC patients were very limited [84–86]. The Phase III AFFIRM trial [85], in patients with mCRPC previously treated with chemotherapy, and the PREVAIL trial [84], in chemotherapy-naïve CRPC patients, provided no ALP data. However, a cohort study of 59 mCRPC patients treated with enzalutamide after docetaxel showed that higher median baseline ALP level was significantly associated with androgen receptor copy number gain ($p = 0.003$) [86]. Although our search results did not identify any additional enzalutamide studies containing ALP data, it is expected that baseline ALP levels would be prognostic for OS if they were evaluated in mCRPC trials with enzalutamide.

Docetaxel

Baseline ALP levels were prognostic for OS in patients with mCRPC treated with docetaxel (Table 2) [8,72,73,87–89]. Although ALP data were not reported in the large Phase III trial (e.g., Southwest Oncology Group [SWOG] 99–16 trial) [90], multivariate analyses [72,73,89] of ALP data from the Phase III TAX327 trial [8] allowed researchers to determine the data's prognostic value. Using a stratified Cox proportional hazards model, it was demonstrated that ALP was one of 10 independent baseline prognostic factors that predicted OS (HR: 1.27 per log rise; $p < 0.0001$) (Table 2) [72]. Another multivariate analysis of TAX327 trial data also demonstrated that low pretreatment ALP levels (continuous or categorical) were prognostic of improved postprogression survival (Table 2) [73].

Subgroup analyses from TAX327 indicated that serum ALP changes were prognostic for OS independent of PSA [74], with normalization of ALP (<120 U/l) remaining prognostic for OS after adjusting for PSA decline $\geq 30\%$ by day 90 (HR: 0.79, 95% CI: 0.65–0.97; $p = 0.022$) (Table 2) [74]. An increase in ALP level remained prognostic for OS after adjusting for PSA increase $\geq 50\%$ by day 90 (HR: 1.69, 95% CI: 1.33–2.14; $p < 0.001$); however, ALP changes during treatment did not meet the criteria for surrogacy for OS. Given that ALP changes did not impact the treatment effect, the authors did not recommend stopping chemotherapy solely on the basis of such changes.

A retrospective analysis of mCRPC patients with bone metastases who had received docetaxel-containing chemotherapy indicated that ALP was a useful biomarker to differentiate PSA flare from early PSA progression after docetaxel treatment [91]. Univariate analysis demonstrated that an initial ALP level decrease ($p = 0.001$) and change in ALP ratio ($p = 0.008$) were significantly associated with a PSA flare. Multivariate analysis confirmed that a decrease in ALP level was an independent predictive factor for PSA flare ($p = 0.017$).

In a retrospective trial in Japanese mCRPC patients receiving docetaxel-based chemotherapy, univariate analysis demonstrated that a baseline ALP level ≥ 300 IU/l was significantly associated with decreased OS (HR: 3.27, 95% CI: 1.70–6.30; $p < 0.01$); this association was not significant in multivariate analysis ($p = 0.76$) [87]. Another retrospective Japanese study, which indicated the prognostic value of baseline ALP, also demonstrated that a combination of hemoglobin, ALP, and age may assist in determining the length of optimal docetaxel regimen for patients with CRPC [92].

The initial report from the Phase III SWOG S0421 trial of docetaxel and atrasentan versus docetaxel and placebo in mCRPC patients ($n = 996$) reported no ALP data [88]; however, in a separate subanalysis ($n = 778$), Cox regression indicated that high baseline ALP level was prognostic for poorer OS (HR: 1.23, 95% CI: 1.14–1.32) [89].

In summary, these studies demonstrate that ALP is a strong baseline prognostic indicator of OS in patients treated with docetaxel and is a potentially useful marker to monitor in patients receiving docetaxel.

Cabazitaxel

ALP data from trials with cabazitaxel in mCRPC patients focused on the prognostic potential of the biomarker [75,76,93]. The TROPIC [93] and CABARESC [76] trials (Table 2) both evaluated the prognostic value of baseline ALP levels in cabazitaxel-treated patients with mCRPC [23,75,76,93]. Although no ALP data were provided in the original publication of the Phase III TROPIC trial [93], multivariate logistic regression analysis of 2-year follow-up data from the trial indicated that low baseline ALP levels were positively prognostic for OS [75]. Univariate and multivariate analyses of the Phase II CABARESC trial also indicated the prognostic value of baseline ALP level for OS [76].

Radium-223

Radium-223 clinical trials evaluated efficacy of the drug in mCRPC patients according to baseline ALP levels, assessed changes in ALP dynamics during treatment, and examined the potential of ALP as a prognostic biomarker [64–66,94–101]. Due to its mechanism of action and the effect of radium-223 on ALP levels during treatment, numerous ALP data were available from mCRPC clinical trials with this agent.

Early Phase I and II trials of radium-223 showed that ALP levels declined in mCRPC patients with bone metastases [94–98], suggesting a role for this variable as a biomarker during radium-223 treatment. The efficacy of radium-223 in reducing and normalizing tALP levels was confirmed in both the Phase III ALSYMPCA trial [64] and the international expanded access program [66]. The Phase III ALSYMPCA trial demonstrated that OS was significantly prolonged with radium-223 compared with placebo in patients with ALP level <220 U/l at baseline (HR: 0.82, 95% CI: 0.64–1.07), as well as those with ALP ≥ 220 U/l at baseline (HR: 0.62, 95% CI: 0.49–0.79) [64].

In an exploratory analysis of ALP, LDH, and PSA dynamics from the Phase III ALSYMPCA trial, analysis using Cox models showed baseline ALP to be a significant prognostic variable for OS (Table 2) [65]. With radium-223, tALP decreases occurred as early as 4 weeks after treatment initiation and remained low until treatment completion at 24 weeks. tALP levels remained significantly lower in the radium-223 group versus the placebo group at all time points to 46 weeks ($p < 0.001$). Radium-223-treated patients with a reduction in tALP from baseline to week 12 had a 55% lower risk of death versus those with no confirmed tALP decline (Table 2). Although tALP declines at 12 weeks correlated with longer OS, they did not meet statistical surrogacy requirements. Proportional treatment effect (PTE) values based on Cox regression models for tALP, LDH, and PSA changes from baseline at week 12 showed that tALP had the highest PTE, but it did not show surrogacy for OS (0.34, 95% CI: 0–0.75); PTE values

for LDH and PSA were 0.07 (95% CI: 0–0.21) and 0 (95% CI: 0–0.08), respectively. The tALP PTE score of 0.34 indicates that the tALP decrease accounted for approximately 34% of the survival benefit from radium-223 treatment [65]. In a separate analysis of the Phase III ALSYMPCA trial, baseline ALP was also a significant variable for the time to the first symptomatic skeletal event according to univariate, but not multivariate, analysis [101].

The radium-223 international expanded access program [66] also indicated the efficacy of radium-223 regardless of baseline ALP level. Median OS was longer for patients with baseline ALP levels <ULN (median: not reached; 95% CI: 16 months–not reached) than for patients with an ALP \geq ULN (median: 12 months; 95% CI: 11–15 months). In an exploratory analysis, patients with a confirmed tALP decline at week 12 had longer OS and longer time to first symptomatic skeletal event compared with those who did not have a confirmed tALP decline [102].

Case reports have correlated changes in skeletal tumor activity on ^{18}F -choline positron emission tomography/computed tomography (^{18}F -choline PET/CT) imaging with ALP levels in patients treated with radium-223 [99,100]. In these cases, reduction of bone-metastatic disease on ^{18}F -choline PET/CT corresponded with decreases in ALP levels.

In summary, these studies demonstrate that ALP level is a strong prognostic indicator of OS, and suggest that ALP is a useful marker to monitor disease activity during radium-223 treatment. Even more so than with the other life-prolonging agents, ALP monitoring during radium-223 treatment is notable, given the lack of correlation between PSA and outcomes.

Using ALP as a biomarker

In patients with mCRPC, changes in ALP level may reflect changes in bone turnover and osteoblastic activity indicative of the extent of bone-metastatic disease [12,17,20]. Decreases in ALP levels were reported to correspond with reduction of bone-metastatic disease on ^{18}F -choline PET/CT imaging [99,100]. More data are needed to evaluate imaging changes and ALP assessments. tALP measurement, which is inexpensive and readily available, can provide valuable insight into changes occurring in the bone and may aid in the diagnosis of bone metastases [18–20]. Serial ALP measurements are useful, regardless of the therapy used to treat mCRPC.

Although clinical studies involving life-prolonging agents in mCRPC have shown that baseline ALP level is prognostic for OS independent of therapy selection, ALP during treatment does not appear to be a confirmed predictive marker for OS. Differences in mechanism of action between the life-prolonging therapies do partly explain ALP dynamics observed during treatment, especially within the initial period after starting a new therapeutic regimen. However, clinical experience is not always reflected in theoretical models and is therefore important to keep in mind. Changes in ALP levels can help decide whether to continue treatment, particularly in the case of discordance between radiologic, clinical, and PSA evaluations.

Clinical experience has shown that ALP levels may increase initially (e.g., first 2–6 weeks) after starting treatment with abiraterone or enzalutamide, and later decrease in mCRPC patients who respond to therapy. This flare in ALP levels is not typically observed during treatment with sipuleucel-T, docetaxel, cabazitaxel, or radium-223. Sipuleucel-T is not expected to have a direct effect on ALP levels, docetaxel and cabazitaxel impact ALP levels indirectly, and radium-223 is expected to rapidly decrease ALP levels during treatment.

Conclusion

ALP is a reasonable prognostic marker that should be routinely monitored in patients with metastatic disease to the bone. Reassuring patients about monitoring changes other than PSA is a crucial part of the clinician's communication with patients and caregivers. It is not recommended that treatment be stopped solely based on changes in ALP; other indicators of disease progression are clearly needed. Continued research investigating the role of ALP as a biomarker is warranted, including evaluating the predictive value of changes in ALP levels during treatment.

Future perspective

As mCRPC treatment strategies continue to evolve, we anticipate that additional biomarkers will be identified to facilitate treatment decisions and that the role of current biomarkers, such as ALP, will be further clarified. The analysis of the predictive value of changes in ALP levels during treatment has until now not been investigated as a prospective end point in clinical Phase III trials, but could, given the retrospective and *post hoc* data mentioned in this review, become a more useful biomarker than any baseline analysis.

Executive summary

Alkaline phosphatase in bone-metastatic castration-resistant prostate cancer

- bALP is an enzyme that is expressed on the surface of osteoblasts; increased levels can indicate either a disease state or healing that is occurring within the bone.
- In the absence of extensive liver disease, bALP is the primary component of serum total ALP (tALP) levels measured in patients with metastatic castration-resistant prostate cancer (mCRPC).
- bALP level is used as a bone turnover marker reflective of a combination of osteoblastic activity and extent of disease (i.e., volume of metastases) in patients with bone-dominant mCRPC.

Clinical importance of ALP

- ALP is a prognostic biomarker in mCRPC, reflecting disease outcome independent of therapy.
- High baseline ALP levels are associated with negative outcomes, including skeletal complications and decreased survival, in patients with mCRPC.
- Baseline ALP is a relevant prognostic marker for overall survival (OS) in bone-dominant mCRPC, along with others (e.g., prostate-specific antigen).
- Changes in ALP levels may reflect changes in bone turnover and osteoblastic activity indicative of the extent of bone-metastatic disease.

Mechanism of action impact on ALP levels

- Six drugs are currently approved for the treatment of mCRPC, based on their ability to prolong survival versus placebo or active comparator in Phase III clinical trials: sipuleucel-T, abiraterone acetate, enzalutamide, docetaxel, cabazitaxel and radium-223 dichloride.
- Differences in mechanism of action between the life-prolonging therapies may partly explain ALP dynamics observed during treatment, especially within the initial period after starting a new therapeutic regimen.

ALP and life-prolonging mCRPC therapies

- Clinical studies involving life-prolonging agents in mCRPC have shown that baseline ALP level is prognostic for OS independent of therapy selection; however, ALP level during treatment does not appear to be a confirmed predictive marker for OS.

Using ALP as a biomarker

- tALP measurement, which is inexpensive and readily available, can provide valuable insight into changes occurring in the bone and may aid in the diagnosis of bone metastases.
- Serial ALP measurements are useful, regardless of the therapy used to treat mCRPC.
- Monitoring ALP levels in mCRPC can provide prognostic information about the likely outcome of the disease, but changes in ALP have not been validated as a surrogate for effectiveness of mCRPC therapy.
- Reassuring patients about monitoring changes other than prostate-specific antigen is a crucial part of the clinician's communication with patients and caregivers.
- It is not recommended that treatment be stopped solely based on changes in ALP; other indicators of disease progression are clearly needed.

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